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(54) Title: NEW COMBINATION

(57) Abstract

The invention provides a composition or kit having as a first active ingredient formoterol, or a salt or solvate derivative thereof, and having as a second active ingredient budesonide, wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:30 to 1:36, and the use of the composition and kit in the treatment of respiratory disorders.

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# NEW COMBINATION

## *Field of the Invention*

The present invention provides a new combination of pharmaceutically active substances which is of use in the treatment of respiratory disorders, particularly asthma.

## *Background to the Invention*

Despite recent advances in the awareness of asthma and the introduction of powerful and effective anti-asthma drugs, asthma remains a poorly understood and frequently poorly treated disease. There have been recent advances in the treatment of the disease which result from the recognition that asthma is a chronic inflammatory disease. Therapy is now aimed at both controlling the symptoms and reducing the inflammation. The symptoms include uncontrolled airway inflammation which may lead to mucosal damage and structural changes possibly leading to irreversible narrowing of the airways and fibrosis of the lungs.

The symptoms may be controlled by $\beta_2$-adrenoreceptor agonists such as salbutamol, salmeterol, terbutaline and formoterol. Formoterol is advantageous because the duration of its effect is long; it has a fast onset time and because it gives few nocturnal wakenings.

Prophylactic therapy is typically provided by steroids such as beclomethasone diproprionate, fluticasone propionate and budesonide. Of these budesonide is advantageous because it may be given in a high inhaled dose (up to 2 mg daily) with very low systemic effects. Long term clinical studies in adults and children have shown that inhaled budesonide has an excellent safety profile.

## *Description of the Invention*

According to the invention there is provided a composition comprising, in an admixture:

(a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate of formoterol, or a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:30 to 1:36, preferably about 1:32.5.

According to the invention there is further provided a kit comprising:

(i) a vessel containing the first active ingredient;

(ii) a vessel containing the second active ingredient; and

(iii) instructions for the sequential or separate administration of the first and second active ingredients to a patient in need thereof;

wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:30 to 1:36, preferably about 1:32.5.

A patient suffering from a respiratory disorder such as asthma can be treated by administering via inhalation a composition according to the invention. Alternatively such a patient can be treated by administering via inhalation, sequentially or separately:

(i) a dose of the first active ingredient; and

(ii) a dose of the second active ingredient;

wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:30 to 1:36, preferably about 1:32.5.

It has been found that the combination of active ingredients according to the invention is advantageous because it gives a significantly improved anti-inflammatory effect compared to known treatments. International patent publication no. WO 93/11773 discloses a combination of budesonide and formoterol having a wide weight ratio range. The closest example of a combination disclosed in this document to the system of the invention has a weight ratio of formoterol fumarate dihydrate to budesonide of 0.06:1, i.e. a molar ratio of 1:16.3. The combination of active ingredients according to the invention gives surprisingly better results when used to treat patients suffering from asthma compared to this known combination.

The first and second active ingredients of the kit can be administered sequentially or separately to treat respiratory disorders. By sequential is meant that the first and second active ingredients are administered one immediately after the other. They still have the desired effect if they are administered separately but less than about 12 hours apart, preferably less than about 2 hours apart, more preferably less than about 30 minutes apart.

Preferably the first active ingredient is administered to provide a daily dose of from 10 to 250nmol (preferably from 15 to 120nmol) and the second active ingredient is administered to provide a daily dose of from 0.1 to 10μmol (preferably 0.2 to 5μmol) or from 39 to 4300μg of the second active ingredient (preferably from 86 to 2150μg), subject to the molar ratio of the first active ingredient to the second active ingredient being within the range of from 1:30 to 1:36.

Suitable physiologically acceptable salts of formoterol include acid addition salts derived from inorganic and organic acids, for example the chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, acetate, succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalene-carboxylate or oleate salts or solvates thereof. The first active ingredient is preferably formoterol fumarate, especially the dihydrate.

When the first active ingredient is formoterol fumarate dihydrate, the preferred daily dose of the first active ingredient is from 4 to 100μg, more preferably from 6 to 50μg (subject to the molar ratio of the first active ingredient to the second active ingredient being within the range of from 1:30 to 1:36).

Most preferably the composition or kit of the invention comprises 6μg of formoterol fumarate dihydrate and 200μg of budesonide, or 4.5μg of formoterol fumarate dihydrate and 160μg of budesonide, either of which is administered up to four times a day.

Alternatively the composition or kit of the invention comprises 12μg of formoterol fumarate dihydrate and 400μg of budesonide, or 9μg of formoterol fumarate dihydrate and 320μg of budesonide, either of which is administered once or twice a day.

Preferably the active ingredient(s) are used in admixture with one or more pharmaceutically acceptable additives, diluents or carriers, preferably in an amount of from 50μg to 25mg per dose, more preferably in an amount of from 50μg to 10mg, most preferably in an amount of from 100 to 2000μg. Examples of suitable diluents or carriers include lactose, dextran, mannitol and glucose. Preferably lactose is used, especially as the monohydrate.

It should be understood that where reference is made to the amounts of each active ingredient that these are metered amounts. When the active ingredients are administered, the amount of each ingredient inhaled by the patient can differ from the metered amount, e.g. due to retention of the active ingredient in the inhalation device. Furthermore when the active ingredients are formulated separately, the administered amount of each is not necessarily reduced proportionately. Thus the administered ratio of the active ingredients could differ from the metered ratio. Preferably the administered ratio is within the metered ratio specified above.

One or more of the active ingredients used in the invention is preferably in the form of a dry powder, more preferably a finely divided, e.g. a micronised, dry powder, e.g. having a mass median diameter of less than 10μm, for example from 1 to 5μm, most preferably an agglomerated micronised dry powder. As an alternative to agglomeration the finely divided active ingredients may be in the form of an ordered mixture with the one or more pharmaceutically acceptable additives, diluents or carriers. An ordered mixture is the combination of finely divided active ingredient with coarse particles of pharmaceutically acceptable additive, diluent or carrier. The ingredients used in the invention can be obtained in these preferred forms using methods known to those of skill in the art.

According to the invention there is further provided the use of a composition or kit according to the invention in the manufacture of a medicament for use in the treatment of a respiratory disorder, e.g. asthma. The invention also provides the use of budesonide or of formoterol in the manufacture of a kit or of a composition according to the invention for use in the treatment of a respiratory disorder, e.g. asthma.

Administration may be by inhalation orally or intranasally. The ingredients are preferably adapted to be administered from a dry powder inhaler, a pressurised metered dose inhaler, or a nebuliser.

When the ingredients of the composition or kit are adapted to be administered from a pressurised inhaler, they are preferably in micronised form. They are dissolved or, preferably, suspended in a liquid propellant mixture. The propellants which can be used include chlorofluorocarbons, hydrocarbons or hydrofluoroalkanes. Especially preferred propellants are P134a (tetrafluoroethane) and P227 (heptafluoropropane) each of which may be used alone or in combination. They are optionally used in combination with one or more other propellants and/or one or more surfactants and/or one or more other excipients, for example ethanol, a lubricant, an anti-oxidant and/or a stabilising agent.

When the ingredients of the composition or kit of the invention are adapted to be administered via a nebuliser they may be in the form of a nebulised aqueous suspension or solution, with or without a suitable pH or tonicity adjustment, either as a unit dose or multidose device.

The composition or kit may optionally be administered as divided doses from 1 to 4, and preferably once or twice a day.

The invention is illustrated by the following Examples which are not intended to limit the scope of the application. In the Examples micronisation is carried out in a conventional manner such that the particle size range for each component is suitable for administration by inhalation. Turbuhaler is a trademark of Astra AB.

*Example 1*

6 Parts by weight of formoterol fumarate dihydrate was mixed with 794 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 200 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

*Example 2*

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 835 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 160 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

*Example 3*

12 Parts by weight of formoterol fumarate dihydrate was mixed with 588 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. 400 Parts by weight of micronised budesonide was added to the conditioned product by mixing and homogenising with a low pressure jet mill. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

*Example 4*

6 Parts by weight of formoterol fumarate dihydrate was mixed with 994 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then

conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

200 Parts by weight of micronised budesonide was mixed with 800 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

*Example 5*

4.5 Parts by weight of formoterol fumarate dihydrate was mixed with 995 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

160 Parts by weight of micronised budesonide was mixed with 840 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

*Example 6*

12 Parts by weight of formoterol fumarate dihydrate was mixed with 988 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

400 Parts by weight of micronised budesonide was mixed with 600 parts by weight of lactose monohydrate. The blend was micronised using a high pressure air jet mill and then

conditioned using the process of EP-A-717 616. The mixture was then spheronised using the process of EP-A-721 331 and filled into the storage compartment of a Turbuhaler.

*Claims*

1. A composition comprising, in admixture:

(a) a first active ingredient selected which is formoterol, a pharmaceutically acceptable salt or solvate thereof, and a solvate of such a salt; and

(b) a second active ingredient which is budesonide;

wherein the molar ratio of (a) to (b) in the composition is from 1:30 to 1:36.

2. A composition according to claim 1, wherein the molar ratio is about 1:32.5.

3. A composition according to claim 1 or 2, wherein the first active ingredient is formoterol fumarate dihydrate.

4. A composition according to claim 1, 2 or 3, additionally comprising a pharmaceutically acceptable additive, diluent or carrier.

5. A composition according to any one of the preceding claims for use in the treatment of a respiratory disorder.

6. A kit comprising

(a) a vessel containing a first active ingredient selected from the group consisting of formoterol, a pharmaceutically acceptable salt or solvate thereof, and a solvate of such a salt; and

(b) a vessel containing a second active ingredient which is budesonide;

(c) instructions for the sequential or separate administration of the first and second active ingredients to a patient in need thereof;

wherein the molar ratio of the first active ingredient to the second active ingredient is from 1:30 to 1:36.

7. A kit according to claim 6, wherein the molar ratio is about 1:32.5.

8. A kit according to claim 6 or 7, wherein the first active ingredient is formoterol fumarate dihydrate.

9. A kit according to claim 6, 7 or 8, additionally comprising a pharmaceutically acceptable additive, diluent or carrier suitable for inhalation.

10. A kit according to any one of claims 6 to 9, wherein each ingredient is in the form of a finely divided dry powder and each vessel is a dry powder inhaler.

11. A method of treating a respiratory disorder, which method comprises administering via inhalation to a patient suffering from the disorder a therapeutically effective amount of a composition as defined in any one of claims 1 to 4.

12. A method of treating a respiratory disorder, which method comprises sequentially or separately administering via inhalation to a patient suffering from the disorder

(a) a dose of a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof, and a solvate of such a salt; and

(b) a dose of a second active ingredient which is budesonide;

wherein the molar ratio of (a) to (b) is from 1:30 to 1:36.

13. Use of a composition according to any one of claims 1 to 4 in the manufacture of a medicament for use in the treatment of a respiratory disorder.

14. Use of a kit according to any one of claims 6 to 10 in the manufacture of a medicament for use in the treatment of a respiratory disorder.

15. Use of formoterol, a pharmaceutically acceptable salt or solvate thereof, and a solvate of such a salt in the manufacture of a composition according to any one of claims 1 to 4 or of a kit according to any one of claims 6 to 10 for use in the treatment of a respiratory disorder.

16. Use of budesonide in the manufacture of a composition according to any one of claims 1 to 4 or of a kit according to any one of claims 6 to 10 for use in the treatment of a respiratory disorder.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/01606

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/57 // (A61K 31/57, 31:165)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, WPI, JAPIO, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 9311773 A1 (AKTIEBOLAGET ASTRA), 24 June 1993 (24.06.93), page 8<br>--<br>-------- | 1-16 |

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 17 December 1997 | 03 -02- 1998 |
| Name and mailing address of the ISA/<br>Swedish Patent Office<br>Box 5055, S-102 42 STOCKHOLM<br>Facsimile No. +46 8 666 02 86 | Authorized officer<br>Gerd Strandell<br>Telephone No. +46 8 782 25 00 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/01606

**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11, 12
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 13 and 14 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/97

International application No.
PCT/SE 97/01606

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9311773 A1 | 24/06/93 | AU 673660 B | 21/11/96 |
| | | AU 3085892 A | 19/07/93 |
| | | CA 2123909 A | 24/06/93 |
| | | CZ 9401434 A | 15/12/94 |
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